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## Domperidone-containing medicines: no longer approved for use in children due to lack of efficacy

Results from a placebo-controlled study in children below the age of 12 years with acute nausea and vomiting using domperidone as an add-on to oral rehydration did not show any difference in efficacy compared with placebo.

Based on these study results, the authorised use of all domperidone-containing products is now restricted to adults and adolescents above the age of 12 years and weighing 35 kg or more.

### Lack of efficacy in the paediatric population

The safety of domperidone-containing products was reviewed in 2014 by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC). At the time there were limited data to support paediatric use in the relief of the symptoms of nausea and vomiting and studies to provide further data to support efficacy in the paediatric population were requested and the results from a placebo-controlled study in children below the age of 12 years with acute nausea and vomiting using domperidone as an add-on to oral rehydration did not show any difference in efficacy compared with placebo. The product information for domperidone-containing medicines will therefore be updated to remove the paediatric posology.

### Reminder on the safe use of domperidone-containing products in accordance with the product information.

Following finalisation of the safety review in 2014, it was concluded that risk minimisation measures were necessary to improve the benefit/risk balance and reduce the risk of serious cardiac adverse events. The HPRA previously communicated the outcome of the EU review in its Drug Safety Newsletter [Edition 61](#) in 2014 and in a reminder article published in 2017 in [Edition 81](#).

### Reminder of indication

- Use of domperidone is restricted to the relief of symptoms of nausea and vomiting in adults and adolescents above the age of 12 years and weighing 35 kg or more.

### Reminder of contraindications

Domperidone is contraindicated in:

- patients with moderate to severe hepatic impairment,
- patients with known existing prolongation of cardiac conduction intervals (particularly QTc)
- patients with underlying cardiac diseases such as congestive heart failure,
- patients with significant electrolyte disturbances,
- during co-administration with QT-prolonging drugs\*
- during co-administration with potent CYP3A4 inhibitors (regardless of their QT-prolonging effects).

\* *Domperidone is contraindicated with QT-prolonging drugs including apomorphine, unless the benefit of co-administration with apomorphine outweighs the risks, and only if the recommended precautions for co-administration mentioned in the apomorphine SmPC are strictly fulfilled.*

### Reminder of the restrictions on dose and treatment duration

- For adults and adolescents over 12 years of age and weighing 35kg or more, the recommended maximum dose in 24 hours is 30mg (dose interval: 10mg up to three times a day).
- Domperidone should be used at the lowest effective dose for the shortest possible duration.
- The maximum treatment duration should not usually exceed one week.

## Key Message

Results from a placebo-controlled study in children below the age of 12 years with acute nausea and vomiting using domperidone as an add-on to oral rehydration did not show any difference in efficacy compared with placebo.

The authorised use of all domperidone-containing products is therefore restricted to adults and adolescents above the age of 12 years and weighing 35 kg or more.

Furthermore, domperidone is associated with an increased risk of serious cardiac adverse reactions.

Healthcare professionals are reminded of the following:

**Therapeutic indications** - Use of domperidone is restricted to the relief of symptoms of nausea and vomiting in adults and adolescents above the age of 12 years and weighing 35 kg or more.

**Contraindications** - Domperidone is contraindicated in patients who have known existing prolongation of cardiac conduction intervals, in patients with significant electrolyte disturbances or underlying cardiac diseases, in patients who are concomitantly taking QT-prolonging drugs or potent CYP3A4 inhibitors and in patients who have moderate or severe hepatic impairment.

**Dose and duration of use** – For adults and adolescents over 12 years of age and weighing 35kg or more, the recommended maximum dose in 24 hours is 30mg (dose interval: 10mg up to three times a day). Domperidone should be taken at the lowest effective dose for the shortest duration possible. Maximum treatment period should not usually exceed one week.

A Direct Healthcare Professional Communication ([DHPC](#)) was circulated by the MAH (following approval by the HPRA) in May 2019 and is available from the HPRA website.

Any suspected adverse reactions should be reported to the HPRA via the available options ([www.hpra.ie](http://www.hpra.ie)).

\* Products currently authorised in Ireland include Motilium and Domerid. Further details are available at [www.hpra.ie](http://www.hpra.ie)

## Direct oral anticoagulants (DOACs)\* are not recommended in patients with antiphospholipid syndrome (APS) due to possible increased risk of recurrent thrombotic events

The European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) recently completed a review of the available data regarding the risk of recurrent thrombotic events in patients diagnosed with antiphospholipid syndrome (APS), treated with direct oral anticoagulants (DOACs). There is currently insufficient evidence that any DOAC offers protection against recurrent thrombotic events in patients with established APS, particularly in those at highest risk. In one randomised open-label multicentre study<sup>1</sup>, rivaroxaban was compared to warfarin in patients with a history of thrombosis, diagnosed with APS and at high risk of thromboembolic events. Thromboembolic events occurred in 12% of patients randomised to rivaroxaban whereas no events were reported in patients randomised to warfarin.

### Advice to Healthcare Professionals

- DOACs are not recommended in patients with APS, particularly high-risk patients (those that test positive for all three antiphospholipid tests – lupus anticoagulant, anticardiolipin antibodies and anti-beta 2 glycoprotein 1 antibodies).
- Patients with APS, in particular high-risk patients, currently receiving a DOAC for prevention of thromboembolic events, should be reviewed to establish whether continued treatment is appropriate. Consideration should be given to switching to a vitamin K antagonist such as warfarin.
- In patients with a history of thrombosis diagnosed with APS, rivaroxaban has been associated with an increased risk of recurrent thrombotic events, compared with the vitamin K antagonist warfarin.
- Other DOACs (apixaban, edoxaban and dabigatran etexilate) may be associated with a similar increased risk of recurrent thrombotic events compared to warfarin.

## Key Message

DOACs are not recommended in patients with APS, in particular high-risk patients (those who test positive for all three antiphospholipid tests).

In patients with a history of thrombosis, diagnosed with APS, the use of rivaroxaban has been associated with an increased risk of recurrent thrombotic events compared to warfarin. Other DOACs may be associated with the same risk.

A Direct Healthcare Professional Communication ([DHPC](#)) was circulated by the MAH (following approval by the HPRA) in May 2019 and is available from the HPRA website.

The product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) for these products will be updated shortly to include a warning regarding APS patients.

Any suspected adverse reactions should be reported to the HPRA via the available options ([www.hpra.ie](http://www.hpra.ie)).\*\*

\* Products currently authorised include apixaban (Eliquis), dabigatran etexilate (Pradaxa), edoxaban (Lixiana) and rivaroxaban (Xarelto). Further details are available at [www.hpra.ie](http://www.hpra.ie) and [www.ema.europa.eu](http://www.ema.europa.eu).

\*\* Rivaroxaban and edoxaban are subject to additional monitoring. Products subject to additional monitoring have a black inverted triangle accompanied by an explanatory statement displayed in their product information (SmPC and PL).

### References

<sup>1</sup> Pengo. V, et al. Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome. *Blood* 2018; 132(13):1365-1371

## Use of Xeljanz (tofacitinib) restricted in patients at high risk of pulmonary embolism while European Medicines Agency (EMA) review is ongoing

The European Medicines Agency's (EMA's) Pharmacovigilance Risk Assessment Committee (PRAC) has commenced a [review](#) of Xeljanz (tofacitinib) following observation of an increased risk of pulmonary embolism (PE) and overall mortality in patients with rheumatoid arthritis taking tofacitinib 10 mg twice daily in an ongoing clinical trial (Study A3921133). As a temporary measure while the review is ongoing, the PRAC has recommended that the 10mg twice daily dose of tofacitinib is contraindicated in patients at high risk for pulmonary embolism.

Xeljanz (tofacitinib) is indicated for the treatment of rheumatoid arthritis and psoriatic arthritis at a recommended dose of 5 mg twice daily. Xeljanz is also approved for treatment of ulcerative colitis at a recommended dose of 10 mg twice daily for induction for 8 weeks and thereafter at a dose of 5 mg twice daily for maintenance.

Study A3921133 is an ongoing open-label clinical trial evaluating the safety of tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily compared with a tumour necrosis factor (TNF) inhibitor in patients with rheumatoid arthritis. The study included patients >50 years of age with at least one additional cardiovascular risk factor.

The preliminary results of the study identified 19 cases of PE out of 3,884 patient-years in the tofacitinib 10 mg twice daily arm of the study compared with 3 cases out of 3,982 patient-years in the TNF inhibitor arm. The overall incidence of PE per patient-year was 6-fold higher in tofacitinib 10mg twice daily arm of the study compared with the TNF inhibitor arm, and approximately 3-fold higher than tofacitinib in other studies across the tofacitinib programme. Additionally, all-cause mortality in the 10 mg twice daily arm was higher compared to the tofacitinib 5mg twice daily and the TNF inhibitor groups. There were 45 deaths from all causes out of 3,884 patient-years in the 10 mg twice daily arm compared with 25 cases out of 3,982 patient-years in the TNF inhibitor group.

### Advice to Healthcare Professionals

While an in-depth review of these risks is ongoing, tofacitinib 10 mg twice daily is contraindicated in patients with one or more of the following risk factors:

- Use of combined hormonal contraceptives or hormone replacement therapy
- Heart failure
- Previous venous thromboembolism, either deep venous thrombosis or pulmonary embolism
- Inherited coagulation disorder
- Malignancy
- Undergoing major surgery

Additionally, other risk factors that should be considered when determining the patient's risk for pulmonary embolism include age, obesity (BMI>30), smoking status and immobilisation.

The recommendation means that, since 10 mg twice daily is the recommended starting dose for ulcerative colitis, patients with ulcerative colitis at high risk of pulmonary embolism should not start treatment with tofacitinib. Patients currently being treated with the 10 mg twice daily dose and who are at high risk of pulmonary embolism should be switched to alternative treatments.

Patients receiving tofacitinib, irrespective of indication, should be monitored for the signs and symptoms of pulmonary embolism, and be advised to seek medical attention immediately if they experience them.

Further information will become available following a detailed review of the benefit-risk balance of Xeljanz in all authorised indications, including whether any further risk minimisation measures should be implemented.

## Key Message

Following observation in a clinical trial of an increased risk of PE and overall mortality in patients treated with 10mg of tofacitinib twice daily for rheumatoid arthritis, the PRAC has commenced a review of the efficacy and safety of tofacitinib in all authorised indications.

While the review is on-going, the 10mg twice daily dose must not be prescribed in patients at high risk of pulmonary embolism

Patients receiving tofacitinib, irrespective of indication, should be monitored for the signs and symptoms of PE, and be advised to seek medical attention immediately if they experience them.

This information has also been communicated to relevant healthcare professionals through a Direct Healthcare Professional Communication (DHPC) circulated by the Marketing Authorisation Holder (MAH), following approval by the HPRAs.

Any suspected adverse reactions should be reported to the HPRAs through the available options ([www.hpra.ie](http://www.hpra.ie)).

\* Further details are available on [www.hpra.ie](http://www.hpra.ie) and [www.ema.europa.eu](http://www.ema.europa.eu)

## Direct Healthcare Professional Communications published on the HPRAs website since the last Drug Safety Newsletter

PRODUCT	SAFETY ISSUE
<a href="#">Modafinal</a>	Potential risk of congenital malformations when administered during pregnancy
<a href="#">Xeljanz (tofacitinib)</a>	Restriction of 10mg twice daily use in patients who are high risk of pulmonary embolism
<a href="#">Domperidone containing products</a>	Removal of paediatric posology and reminder of indication and contraindications related to serious cardiac side effects
<a href="#">Direct Oral Anticoagulants (DOACs)</a>	Not recommended in patients with antiphospholipid syndrome due to possible increased risk for recurrent thrombotic events
<a href="#">Lapatinib (Tyverb)</a>	Important update to Summary of Product Characteristics (SmPC)
<a href="#">Lemtrada (alemtuzumab)</a>	Restriction of use due to serious safety concerns

Correspondence/Comments should be sent to the Pharmacovigilance Section, Health Products Regulatory Authority, contact details below.